REMARKS

1. Claim Amendments

Claim 40 has been rewritten in independent form.

2. Indefiniteness Issues (112 ¶4)

Claim 40 is rejected under 35 U.S.C. 112, 4th paragraph, as being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends.

The examiner asserts that claim 40 recites that the administering step comprises *immunizing* an individual. The examiner asserts that the present specification makes no distinction between "administering" and "immunizing" per se, and the terms are often used interchangeably throughout the disclosure. Therefore, the examiner is of the opinion that it is unclear how the step of "immunizing" of claim 40 limits the "administering" of claim 39.

In response, the claim has been rewritten in independent form. This rejection is now therefore moot.

3. Prior Art Issues

3.1. Claims 39-43, 49 and 52-55 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 01/52878 by Eisenbach-Schwartz et al. (published Jul. 26, 2001), as evidenced by the Wikipedia entry for "Aluminum hydroxide", downloaded Aug. 18, 2011.

The examiner asserts that Eisenbach-Schwartz et al. teach a method of treating injury to, or diseases of, the central nervous system comprising administering Copolymer 1 (Cop 1), a Cop 1-related peptide or polypeptide, or activated T cells that recognize an antigen of Cop 1 or a Cop 1-related peptide or polypeptide.

The examiner further asserts that Eisenbach-Schwartz teaches that in one embodiment, Cop 1 or a Cop 1-related peptide or polypeptide is administered in methods for protecting CNS cells from glutamate toxicity or for treating injury or disease caused or exacerbated by glutamate toxicity (see p. 24, lines 25-29).

According to the examiner, Eisenbach-Schwartz notes that in light of the findings with respect to the glutamate protective aspect of the disclosed invention, clinical conditions that may be treated in accordance with the disclosed invention include anxiety and psychosis (see p. 34, lines 5-9). The examiner asserts that Eisenbach-Schwartz further comments that protection against glutamate toxicity can also be achieved using Cop 1-related T cell treatment (see p. 34, lines 17-20).

Hence, the examiner is of the opinion that the reference teaches treating a patient having psychosis comprising administering Cop 1, a Cop 1-related peptide or polypeptide, or T cells activated by Cop 1 or a Cop 1-related peptide or polypeptide, and that such teaching is relevant to claims 39 and 49 with respect to treatment of a schizophrenia related disorder, such as a brief psychotic disorder. According to the examiner, these teachings are also relevant to the specific agents as recited in present claims 41-43.

With respect to claims 40 and 52-55, the examiner asserts that Eisenbach-Schwartz discloses that pharmaceutical compositions comprising Cop 1 or Cop 1-related peptide or polypeptide may optionally be administered with an adjuvant, such as alum, in the usual manner for immunization (see p. 40, lines 1-5). The examiner is of the opinion that since Eisenbach-Schwartz teaches that the use of an adjuvant is optional, this would account for administration of Cop 1 without an adjuvant, as in claim 53. The examiner alleges that

the teachings of Eisenbach-Schwartz provide for the presently recited invention of claims 39-43, 49 and 52-55.

In response, applicant notes that although Eisenbach-Schwartz discloses that clinical conditions that may be treated in accordance with the disclosed invention include anxiety and psychosis, according to the A.D.A.M. Medical Encyclopedia. Atlanta (GA): A.D.A.M.; 2011, as published on the NCBI website (copy enclosed), "psychosis" is "a loss of contact with reality, usually including false beliefs about what is taking place or who one is (delusions) and seeing or hearing things that aren't there (hallucinations)". In contrast, "schizophrenia" is a "complex mental disorder that makes it difficult to tell the difference between real and unreal experiences, think logically, have normal emotional responses, and behave normally in social situations".

This encyclopedia further asserts that psychosis is also associated with a number of psychiatric disorders, including bipolar disorder (manic or depressed), delusional disorder, depression with psychotic features, personality disorders (schizotypal, shizoid, paranoid, and sometimes borderline), schizoaffective disorder and schizophrenia.

No advantage was claimed specifically for the treatment of schizophrenia in Eisenbach-Schwartz and therefore Eisenbach-Schwartz cannot anticipate the present application.

Reconsideration and withdrawal of this rejection is therefore respectfully urged.

3.2. Claim 48 is rejected under 35 U.S.C. 103(a) as being obvious over WO 01/52878 by Eisenbach-Schwartz et al. (published Jul. 26, 2001) in view of Farber et al. (Mol Psychiatry, 2002; 7(1):32-43).

The examiner is of the opinion that the difference between the teachings of Eisenbach- Schwartz and the presently claimed invention is that the prior art reference does not

teach that the psychosis is schizophrenia.

The examiner asserts that Farber et al. teach that NMDA receptor hypofunction (NRHypo)-induced neurotoxicity may underlie neurodegeneration and psychosis in diseases such as Alzheimer's disease and schizophrenia (see abstract). The examiner explains that the NMDA receptor is a receptor for glutamate and thus is responsible for excitatory glutamatergic signaling in the CNS.

The examiner is of the opinion that it would have been obvious to one of ordinary skill in the art at the time the invention was filed to have modified the teachings of Eisenbach-Schwartz to treat patients having schizophrenia by administering Cop 1. The examiner asserts that the skilled artisan would have been aware of the teachings of Eisenbach-Schwartz, for example, which state that psychosis can be treated by using Cop 1 because of the neuroprotective effects of Cop 1 against glutamate toxicity. The examiner asserts that in view of the teachings of Farber et al., the ordinary skilled artisan would have also recognized that schizophrenia, which is a specific type of psychosis, is associated with glutamate receptor-induced neurodegeneration (i.e., glutamate-related neurotoxicity).

The examiner is therefore of the opinion that it would have been obvious to use an agent (Cop 1) taught to be useful in abrogating glutamate toxicity for the treatment of psychosis for the treatment of such pathology in schizophrenia, because the skilled artisan would have had good reason to pursue the known options within his or her technical grasp to yield (allegedly) predictable results. The examiner alleges that psychosis is the main component of schizophrenia, and therefore such would amount to the simple substitution of one know element (i.e., psychosis) for another (i.e., schizophrenia) to obtain predictable results.

Applicant agrees with the examiner that Eisenbach-Schwartz does not teach that psychosis is schizophrenia, and would like again to bring the examiner's attention to the fact that psychosis is part of a number of psychiatric disorders, including bipolar disorder (manic or depressed), delusional disorder, depression with psychotic features, personality disorders (schizotypal, shizoid, paranoid, and sometimes borderline), schizoaffective disorder and schizophrenia. Therefore, the examiner is incorrect in interpreting the term "psychosis" as meaning "schizophrenia" for the purpose of examination. This flies in the face of the dictionary definitions provided above. Eisenbach-Schwartz does not specify treatment of schizophrenia and no advantage was claimed in Eisenbach-Schwartz, specifically for the treatment of schizophrenia.

Furthermore, Farber et al does not teach that schizophrenia is associated with glutamate receptor-induced neurodegeneration (i.e., glutamate-related neurotoxicity). Instead, Farber et al teach (p. 32, left column):

> Excessive activation of NMDA glutamate receptors triggers neuronal degeneration in acute brain injury conditions, such as stroke, head trauma and epilepsy, and NMDA antagonists confer protection against such degeneration. However, NMDA antagonists have significant side effects. In adult humans they trigger psychosis, and in adult rats they produce neurotoxicity [Emphasis added].

It follows that the psychosis is triggered by the very agents used to treat neurodegeneration caused by glutamate toxicity - not by the glutamate toxicity. Therefore, it is misleading to assert that that schizophrenia is associated with glutamate receptor-induced neurodegeneration and to allege that it is associated with glutamate-related

neurotoxicity. Thus, the ordinary skilled artisan, even if aware of Farber et al, would have no reason to believe that schizophrenia is associated with glutamate receptor-induced neurodegeneration, and therefore would have no motivation to combine the teachings of the two publications.

Reconsideration and withdrawal of this rejection is therefore respectfully urged.

3.3. Claims 39-43, 48, 49 and 52-55 are rejected under 35 U.S.C. 103(a) as being obvious over Wank (Med Hypotheses, 2002; 59(2):154-158) in view of Ziemssen et al. (Brain, 2002 Nov; 125:2381-2391) and WO 01/52878 by Eisenbach-Schwartz et al. (published Jul. 26, 2001) as evidenced by the Wikipedia entry for "Aluminum hydroxide", downloaded Aug. 18,2011.

The examiner asserts that Wank teaches that schizophrenia and other psychiatric disorders can be treated by adoptive immunotherapy, and that, in particular, Wank discloses that activation of all T lymphocytes reactivates those downregulated by low-grade chronic infections and restores equilibrium in immune cell populations. The examiner further asserts that different immune cell subpopulations express different neurotrophin receptors and produce different neurocytokines, particularly brain-derived neurotrophic factor (BDNF) and neurotrophin 3 (NT-3), which Wank notes appear to play important roles in schizophrenia and bipolar disorder (see abstract).

The examiner is of the opinion that the difference between the teachings of Wank and the presently claimed invention is that Wank does not teach that the activated administered T cells were stimulated by Copolymer 1 or a Cop 1-related peptide or polypeptide, or that the activation of T cell occurs in vivo by immunizing the patient with a vaccine comprising Cop 1 or a Cop 1-related peptide or polypeptide, with or without an adjuvant.

The examiner then asserts that Ziemssen et al. teach that glatiramer acetate (GA; also known as Copolymer 1), which is a pan T-helper (TH) cell activator, induces T cells to produce BDNF, and that Ziemssen comments that the beneficial effects of GA-activated T cells might be due to their release of BDNF at the site of neuronal injury.

The examiner further asserts, *inter alia*, that Eisenbach-Schwartz notes that in light of the findings with respect to the glutamate protective aspect of Cop 1 therapy, psychosis may be treated in accordance with the disclosed invention (see p. 34, lines 5-9), and that protection against glutamate toxicity can also be achieved using Cop 1-activated T cell treatment (see p. 34, lines 17-20). The examiner concludes that the reference teaches treating a patient having psychosis comprising administering Cop 1, a Cop 1-related peptide or polypeptide, or T cells activated by Cop 1 or a Cop 1-related peptide or polypeptide, which is allegedly relevant to claims 39 and 49 with respect to treatment of a schizophrenia related disorder, such as a brief psychotic disorder and that these teachings are also relevant to the specific agents as recited in present claims 41-43.

Applicant notes that Wank reports on a single patient with schizophrenic disorder. One of ordinary skill in the art would cast doubts on conclusions reached on the basis of results obtained from a single individual, certainly in view of the fact that the patient is medicated with fluphenazindecanoat and azithromycine in addition to the immunotherapy. Indeed, the skilled artisan would expect adoptive immunotherapy to be beneficial in the treatment of schizophrenia only in conjunction with additional agents, because Wank teaches that "Adoptive immunotherapy had the role of an adjuvant therapy" (emphasis added; page 155, right column, last sentence in second paragraph from the bottom).

Furthermore, Wank, teaching the principle of adoptive immunotherapy, asserts that

> the patient's immune cells get stimulated outside the body, in vitro. Monoclonal antibodies against the signal transducing CD3 polypeptide complex activate all T lymphocytes" (p. 55, left column, 3rd paragraph).

Applicant notes that CD3-activated T lymphocytes are activated in a general manner, and not against a specific antigen. Therefore, these T cells are incapable of homing to a specific site and will remain in the peripheral blood.

Thus, the examiner's acknowledgment that the difference between the teachings of Wank and the presently claimed invention is that Wank does not teach that the activated administered T cells were stimulated by Cop 1 or a Cop 1-related peptide or polypeptide, or that the activation of T cell occurs in vivo by immunizing the patient with a vaccine comprising Cop 1 or a Cop 1-related peptide or polypeptide, with or without an adjuvant, has great importance, because this difference provides a conceptual gap between Wank and the present application that could not have been bridged by the skilled artisan.

The conceptual difference is that while the present invention specifically stimulates the T cells in a way that enables them to home to the CNS, accumulate at the site of injury and acquire a neuroprotective phenotype, Wank's T cells, which are stimulated in a non-specific way, stay put in the peripheral blood and can have only marginal influence, if any, on the CNS. The reason that Cop 1 stimulated T cells home to injured CNS tissue is explained in the description of e.g. Eisenbach-Schwartz:

In the laboratory of the present inventors, it has

> recently been discovered that activated T cells that recognize an antigen of the nervous system (NS) of the patient promote nerve regeneration or confer neuroprotection… More specifically, T cells reactive to MBP were shown to be neuroprotective in rat models of partially crushed optic nerve (Moalem et al, 1999) and of spinal cord injury (Hauben et al, 2000) (p.5, lines 19-28).
>
> The mechanism of action of such NS-specific T cells has yet to be discovered, but the massive accumulation of exogenously administered T cells at the site of CNS injury suggests that the presence of T cells at the site of injury plays a prominent role in neuroprotection. It appears, however, that the accumulation, though a necessary condition, is not sufficient for the purpose, as T cells specific to the non-self antigen ovalbumin also accumulate at the site, but have no neuroprotective effect (Hirschberg et al, 1998) (p. 7, lines 7-15).
>
> Studies have demonstrated partial cross-reactivity of Cop 1 with MBP at both the T cell (Webb et al, 1973) and the antibody (Teitelbaum et al, 1988) level. Cop 1 can serve as an antagonist of the T-cell antigen receptor for the MBP immunodominant epitope (Aharoni, 1998). It can also bind to various MHC class II molecules and prevent them from binding to T cells with specific antigen-recognition properties (Fridkis-Hareli et al, 1999a) (p. 8, lines 9-24).

Thus, Cop-1 activated T cells are capable of accumulating in the CNS at the site of injuries and become activated there and acquire neuroprotective functions due their cross reactivity with antigens expressed at the site, as taught in

Eisenbach-Schwartz, but Wank et al does not teach that the activated T cells can home in to the CNS, and even if the cells would home in to the CNS, they would not be neuroprotective because they would not cross-react with local antigens. Furthermore, Eisenbach-Schwartz does not teach that the CNS damaged in a brain of patient with schizophrenia expresses antigens that cross-react with Cop-1. In fact, Eisenbach-Schwartz does not even teach that the damaged brain in patient with psychosis expresses antigens that cross-react with Cop-1.

The examiner also cites Ziemssen et al. that teach that glatiramer acetate induces T cells to produce BDNF. Applicant notes that the inventors were well aware of this and that the description of the present application (Example 6, paragraph [0116]) discloses:

> Several research groups have reported that T cells reactive to Cop-1 home to sites of pathology in the CNS (Kipnis et al., 2000; Aharoni et al., 2002), and that activated Cop-1-reactive T cells, being able to cross-react with various CNS-related self-antigens, can produce neurotrophic factors such as BDNF (Kipnis et al., 2000; Aharoni et al., 2002; Kerschensteiner et al., 2003), which is known for its ability to confer neuroprotection to injured CNS tissue. BDNF deficiency has been reported in patients with schizophrenia (Weickert et al., 2003, Egan et al., 2003); it is unclear, however, whether the deficiency is a cause or an effect, and whether BDNF-based treatment will be beneficial.

Production of neurotrophic factors by T cells depends on the state of activation of the T cells (Moalem et al., 2000). Production of neurotrophic factors by Cop-1-reactive T cells therefore evidently requires a

> local signal from resident antigen-presenting cells that these T cells can recognize. We therefore carried out an experiment in vitro to determine whether Cop-1-reactive T cells, on encountering CNS myelin, can produce BDNF. [emphasis added].

Thus, since it was not clear whether BDNF is beneficial in treating schizophrenia, there would be no motivation to cause T cells to accumulate at the site of injury in the schizophrenic brain and produce there BDNF. Furthermore, as noted above, production of neurotrophic factors by Cop-1-reactive T cells requires a local signal from resident antigen-presenting cells that these T cells can recognize. However, Ziemssen et al. does not teach whether such a local signal is transduced to the T cells in schizophrenia lesions, and neither do Eisenbach-Schwartz nor Wank. Thus, it is unpredictable whether the Cop-1 activated T cells would produce BDNF at the schizophrenia lesions (the present application (paragraph [0003]) teaches that in the brain of schizophrenia patients there is loss of hippocampal volume and death of hippcampal neurons).

In a different but related matter, Applicant notes that Ziemssen et al. also teach (page 125, Summary):

> "As the signal-transducing receptor for BDNF, the fulllength 145 tyrosine kinase receptor (trk) B, is expressed in multiple sclerosis lesions, it is likely that the BDNF secreted by GA-reactive TH2 and TH1 has neurotrophic effects in the multiple sclerosis target tissue."

However, Ziemssen et al. does not teach whether trkB is expressed in schizophrenia lesions in the hippocampus or dorsolateral prefrontal cortex (see the description of

the present application (paragraph [0003]) and neither do Eisenbach-Schwartz nor Wank. The examiner is of the opinion that the beneficial effects of GA-activated T cells might be due to their release of BDNF at the site of neuronal injury; however, the lack of information regarding the expression of trkB in schizophrenia lesions would make it unpredictable, if one assumes that Cop-1 activated T cells would accumulate at the site of injury in the schizophrenic brain and acquire neuroprotective features, whether the BDNF that may be released by these T cells at the site of injury would have any effect at all.

Thus, the skilled artisan would not have had reasonable expectation of success in trying to treat schizophrenia by administering Cop-1 or Cop-1 activated T cell, and therefore claims 39-43, 48, 49 and 52-55 cannot be made obvious by a combination of Wank, Ziemssen et al. and Eisenbach-Schwartz as evidenced by the Wikipedia entry for "Aluminum hydroxide. Reconsideration and withdrawal of this rejection is therefore respectfully urged.

4. Provisional Double Patenting Issues

Claims 39-42, 49 and 52-55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 5, 6, 9, 10 and 15 of copending Application No. 12/437,167.

The examiner asserts that although the conflicting claims are not identical, they are not patentably distinct from each other because in each case the claims recite the administration of an immunizing composition of Copolymer 1, a Copolymer 1-related peptide or polypeptide, or T cell that have been activated by Copolymer 1 or a Copolymer 1-related

peptide or polypeptide to an individual for therapy.

Since this is a provisional obviousness-type double patenting rejection applicant respectfully requests that this provisional rejection be either held in abeyance until such time that the conflicting claims of copending application no. 12/437,167 are patented before the claims of the present application, or withdrawn if the present application is deemed allowable, but for the provisional double patenting rejection, before allowance of the reference application. See MPEP 804(I)(B)(2), second paragraph. Note that the instant application is the earlier filed application.

Respectfully submitted,

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Enclosures
-"psychosis", ADAM Medical encyclopedia (2011), available online at www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002520
-"Schizophrenia", ADAM Medical Encyclopedia (2011), available online at www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001925

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